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Growth Hormone Deficiency and Excessive Sleepiness: A Case Report and Review of the Literature

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Abstract

The somatotropic axis is intricately involved in normal sleep, as evidenced by the fact that hypothalamic growth hormone-releasing hormone (GHRH) has sleep promoting effects and pituitary growth hormone (GH) release is strongly associated with slow-wave sleep (SWS). Abnormalities in the somatotropic axis, such as GH deficiency of hypothalamic or pituitary origin, result in an alteration of normal sleep patterns which may explain the fatigue reported in these individuals. Sleep disorders such as narcolepsy, in which individuals abnormally enter rapid eye movement (REM) sleep at sleep onset are also associated with an altered GHRH circadian rhythm and abnormal GH secretion. While few studies are available, this review explores what is known about sleep abnormalities in GH deficiency, the effect of treatment on sleep in patients with GH deficiency, and GH secretion in narcolepsy. Emerging evidence suggests a hypothalamic link between narcolepsy and GH secretion. We also describe the unique constellation of isolated idiopathic GH deficiency and severe excessive sleepiness in adopted Nicaraguan siblings, one of which has narcolepsy and the other idiopathic hypersomnia.

Keywords

Growth Hormone Deficiency; Narcolepsy; Idiopathic Hypersomnia; Slow-wave Sleep

Background: Somatotropic Axis and Sleep

Normal sleep consists of two stages: REM and non-REM sleep which alternate cyclically (1). Non-REM sleep consists of stages 1, 2, 3, and 4, each of which has its own unique brain activity (2). Stages 3 and 4, which predominantly happen during the first third of nightly sleep, are known as SWS and are considered the deep stages of sleep (3). Non-REM begins first, progresses through its stages, and subsequently REM sleep occurs (1).

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It is well known that pituitary GH is secreted in a pulsatile fashion primarily during sleep and reaches its highest amplitude during SWS (4–6). This release occurs secondary to stimulation by hypothalamic GHRH which results in significantly increased GH secretion (7). GHRH given during SWS, as opposed to during REM sleep or an awakened state, results in a larger GH response (8). GHRH itself has sleep promoting effects (9) and in healthy young adult males its episodic rather than continuous administration increases SWS duration (7, 10). In the rodent model, this sleep promoting effect has been shown to occur independent of GH (11). While GHRH's effect on GH release and promotion of SWS occur through distinct hypothalamic neurons, these processes are not completely independent, but instead are quite interconnected (12, 13).

Some have hypothesized that in pituitary GH deficiency, the lack of negative feedback inhibition of GH on GHRH leads to increased activity of GHRH and the subsequent promotion of excessive SWS (14). In contrast, patients with a hypothalamic origin may have deficient SWS and REM sleep due to the combination of GHRH and GH deficiencies (15).

Indeed, subjects with isolated GH deficiency have been shown to have decreased duration of SWS (16) and REM sleep (17) which corrects with appropriate GH replacement (18, 19). In a study with 18 healthy young adults, GH administration decreased SWS, but increased REM sleep (20).

These studies suggest that since the somatotropic axis is intricately involved in normal sleep, abnormalities may contribute to the fatigue reported in individuals with GH deficiency (21, 22). With the paucity of data, further studies are needed to clarify this potential relationship.

Case Report

An 8 4/12 year old Hispanic boy and his 6 6/12 year old sister were referred for pediatric endocrinology evaluation due to poor growth. Both had been adopted from a Nicaraguan orphanage 2 years earlier where they had been placed due to emotional and physical neglect. Both had a history of severe malnutrition which had resolved by the time of our evaluation. Additional history consisted of debilitating fatigue and a pattern of sleeping ~18 hours a day, rendering it impossible for them to attend school or have a normal life.

On physical exam, heights were at −2.17 SD (boy) and −3.25 SD (girl) with BMIs at −1.38 SD (boy) and −1.04 SD (girl). Evaluation revealed low serum IGF-1 levels of 20 ng/ml and 15 ng/ml and stimulation testing demonstrated peak GH levels of 2.39 ng/dl and 4.31 ng/dl in the boy and girl, respectively. Pituitary MRIs were normal. Bone age xrays were delayed at ~−3 SD in the boy and −4 SD in the girl. Thyroid function tests and AM cortisol were normal. GH therapy was started at 0.3 mg/kg/wk and growth velocity improved from 0 to 7.92 cm/yr (boy), and from 2 to 5.56 cm/yr (girl) during the first 6 months of therapy. IGF-1 levels normalized in both.

Both entered puberty spontaneously at age 11 11/12 years (boy) and 10 8/12 years (girl). GH therapy was weight-adjusted and most recent growth parameters have improved with height −1.33 SD, BMI of −0.12 SD, growth velocity of 11.2 cm/yr, and bone age consistent with chronological age at −0.25 SD in the boy and height −1.02 SD, BMI of −0.05 SD, growth

velocity of 14.8 cm/yr, and a delayed bone age of −3SD in the girl. The children's growth charts are shown in Figure 1.

While on GH therapy, the mother reported worsening hypersomnia prompting referral to sleep medicine where the boy was diagnosed with narcolepsy and the girl with idiopathic hypersomnia. Both were started on modafinil, transitioned to armodafinil, and finally sodium oxybate due to poor response. With this most recent regimen, their excessive sleepiness has improved.

Genetic testing has been inconclusive. Whole exome sequencing revealed a previously unreported variant in one of two copies of the CPA1 gene (c.497 G>T (p.G166V)) of uncertain significance in both siblings. Other variants in this gene have been associated with pancreatic disease, but there is no evidence of pancreatic issues in these siblings. Mitochondrial DNA sequencing and metabolic evaluation were negative. Interestingly, testing did reveal that they are half-siblings.

Discussion

Sleep Abnormalities in GH deficiency

There are few human studies that have examined sleep quality in individuals with GH deficiency. In one, 30 untreated adult subjects with GH deficiency were compared to 30 matched controls (14). Compared with controls, subjects with GH deficiency had poorer sleep quality determined by the Pittsburgh Sleep Quality Index and also had lower quality of life scores. Those with pituitary GH deficiency had a longer duration and more intense SWS, while those with hypothalamic GH deficiency had lower intensity SWS. A sleep study using wrist actigraphy and polysomnography in 9 adults with GH deficiency showed decreased sleep duration and increased sleep fragmentation compared to 9 healthy controls (13). Children with GH deficiency also have different sleep characteristics. In a study of 10 children with GH deficiency compared with 20 matched controls, those with GH deficiency had abnormal sleep macrostructure (decreased sleep duration, sleep efficiency, movement time, stage 2 non-REM sleep, and percent REM sleep) and altered sleep microstructure (reduced arousal instability) (23).

Effect of Treatment on Sleep in GH Deficiency

In 13 adults with GH deficiency of confirmed or likely pituitary origin, after 4 months of GH replacement therapy, there was a significant decrease in sleep duration primarily due to decreased SWS intensity and an earlier wake time (24). Several had panhypopituitarism with and without surgery or radiotherapy and etiologies of GH deficiency varied among subjects and included idiopathic, as well as organic causes. A significant decrease in stage 3 of SWS was also seen after GH therapy in 6 of 7 children with GH deficiency (25). Five of these children had idiopathic, isolated GH deficiency, one had septo-optic dysplasia, and one developed hypopituitarism after resection and radiation therapy for craniopharyngioma. Both of these studies suggest that GH replacement deceases SWS, adding support for the hypothesis that in pituitary GH deficiency, lack of negative feedback of GH results in unopposed GHRH with consequent SWS excess.

However, other studies have found no difference in sleep in treated subjects with GH deficiency (26, 27). In a randomized double-blinded placebo controlled trial over 6 months, day and nighttime sleep EEG recordings and a multiple sleep latency test were performed at baseline and after 6 months of GH therapy in 17 adults with GH deficiency and no sleep effect of therapy was found (26). The etiology in the majority of subjects was a pituitary adenoma with subsequent pituitary surgery and occasionally radiation therapy. Thus, it is difficult to draw clear conclusions regarding the impact of GH treatment on sleep.

Narcolepsy and Growth Hormone Secretion

Narcolepsy is a sleep disorder characterized by excessive daytime sleepiness, abnormal REM sleep including episodes with loss of muscle tone (cataplexy), sleep paralysis, and hypnagogic hallucinations (28). Type 1 narcolepsy is defined by cataplexy and results from extensive loss of the hypothalamic neurons that secrete the neurotransmitter hypocretin (also known as orexin) (29–31). Type 2 lacks cataplexy and the cause is unknown (28). While non-REM sleep normally occurs first, those with narcolepsy enter directly into REM sleep at sleep onset (32). Idiopathic hypersomnia is considered a diagnosis of exclusion once other causes of excessive daytime sleepiness have been ruled out (33). Features of idiopathic hypersomnia include extreme fatigue after awakening from sleep, high sleep efficiency (time spent in bed asleep), and shortened sleep latency (length of time from awakened state to sleep onset) (33, 34).

While the presence of GH deficiency in narcolepsy has not been investigated, there are a few small studies that have explored 24-hour GH secretion in this condition. In 4 adult subjects with narcolepsy, the GH peak during SWS was absent or greatly decreased (35) compared with the substantial GH peak within 60 minutes of sleep onset that was observed in 4 healthy controls. Other studies have demonstrated that people with narcolepsy do not have deficient, but rather dysregulated GH secretion that is not clearly linked with sleep stages (36). GH secretion and sleep patterns were assessed over 24 hours in 7 adult individuals with narcolepsy with confirmed hypocretin deficiency and compared to matched controls (37). Basal and pulsatile GH secretion and GHRH-induced GH secretion were similar between subjects with narcolepsy and controls, but those with narcolepsy secreted about 50% of their total daily GH during the day vs only 25% in the controls.

Short stature and GH deficiency are not known features of narcolepsy. One study has described anthropometric and endocrine data in 72 pediatric subjects with type 1 narcolepsy over a 1-year follow up period (38). In the 39 subjects who underwent GH stimulation testing with arginine and clondinine, 23 had a blunted GH concentration defined by a peak level below 8 ng/mL on at least one of the two provocative tests. All had normal IGF-1 z-scores and all children were of normal height (mean z-score 0.72 +/− 1.07) and appropriate for their genetic potential, suggesting a normal functioning GH axis. Growth velocity was low only in the subgroup close to completion of puberty which is expected for this pubertal stage. While linear growth appears normal, other endocrinopathies that have been reported in the setting of narcolepsy are precocious puberty and obesity (38, 39).

Table 1 summarizes features of the somatotropic axis as it relates to GH deficiency, narcolepsy, and the normal state.

Hypothalamic Link

While there appears to be a link between abnormalities in the somatotropic axis and sleep regulation, evidence supporting a hypothalamic link between narcolepsy and GH deficiency is beginning to emerge. The hypocretin, orexin-A, was shown in rat models of GH deficiency (hypophysectomized and Lewis dwarf rat) to decrease GHRH expression in the paraventricular nuclei (40). Another study using adult male rats demonstrated that administration of orexin-A decreased spontaneous GH secretion (41). Hypothalamic somatostatin is well-known to inhibit GH release as part of normal physiology (42) and orexin-A stimulated somatostatin release in male rats (43). These studies may explain the disrupted circadian rhythm of GHRH (37) and abnormal GH secretion in humans with narcolepsy (35, 44). Considering the complexity of the GH system, additional cross-connections involving hypocretins or other modulators of the somatotropic axis likely exist.

Conclusion

To the best of our knowledge, our siblings represent the first report of GH deficiency in the setting of narcolepsy and idiopathic hypersomnia. We propose that hypothalamic dysfunction may be the link between GH deficiency and sleep disorders in these children. It is unclear why the siblings developed increased sleepiness following initiation of GH therapy as existing reports have found no effect or an improvement in sleep in subjects receiving GH treatment, albeit none of these studies included cases of narcolepsy or idiopathic hypersomnia. Further studies, particularly in humans are needed to clarify the relationship between GH, narcolepsy, and sleep disorders.

Disclosure

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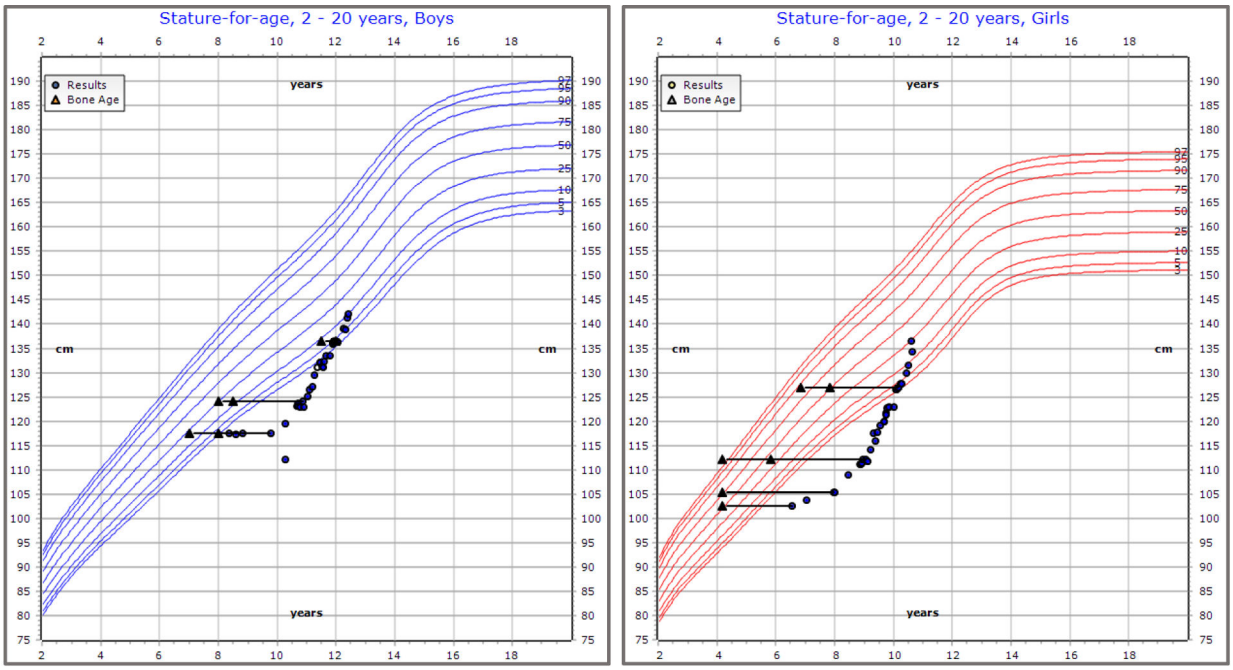

Figure 1.
Growth charts for boy (left) and girl (right). Δ indicates bone ages.

Table 1.

Established and proposed relationships between the somatotropic axis and sleep in normal physiology, GH deficiency, and narcolepsy.

Normal Sleep	GH Deficiency	Narcolepsy
• GHRH increases SWS duration • GH primarily secreted during SWS (Stages 3 & 4)	• Hypothalamic origin – Deficient SWS and REM sleep • Pituitary origin – Lack of negative feedback of GH on GHRH → increased GHRH → promotion of SWS	• GH peak during SWS absent or decreased • 24-hour secretion not deficient – Not clearly linked with sleep stages – Greater percentage of secretion during daytime than controls